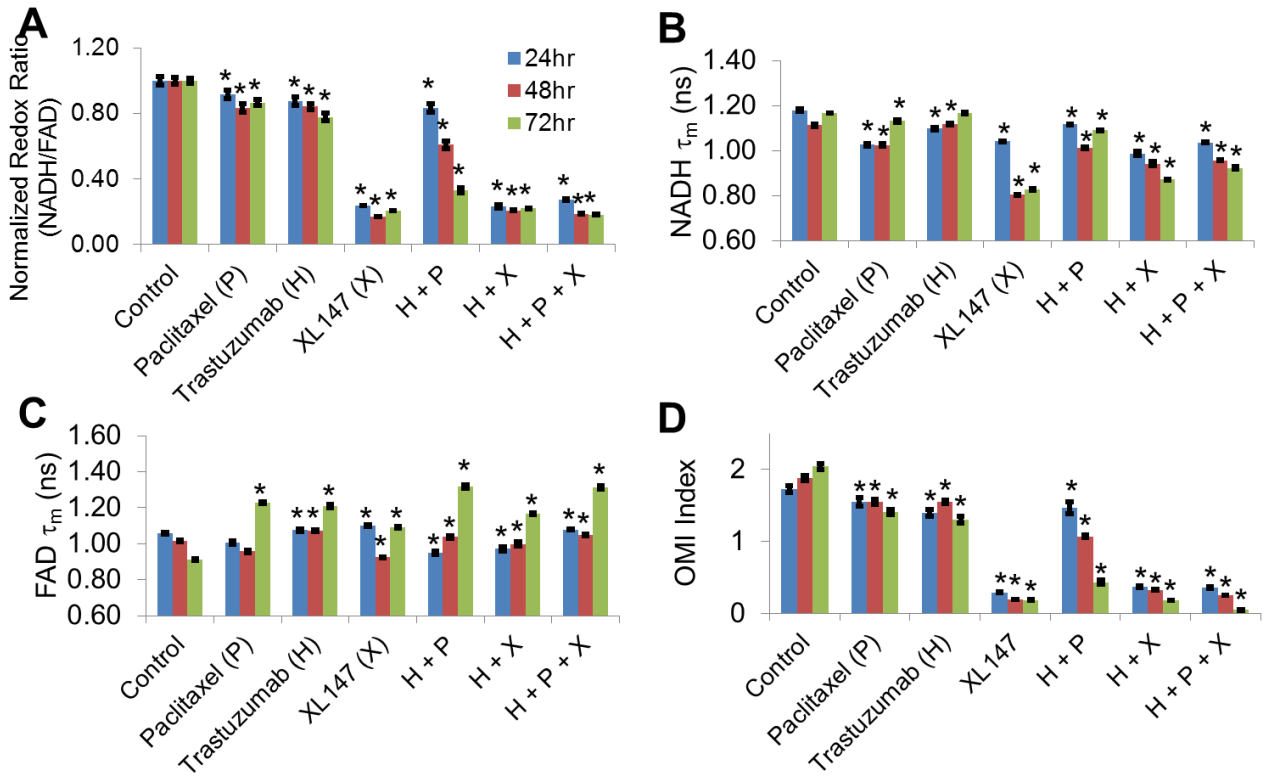
Supplementary Tables and Figures:



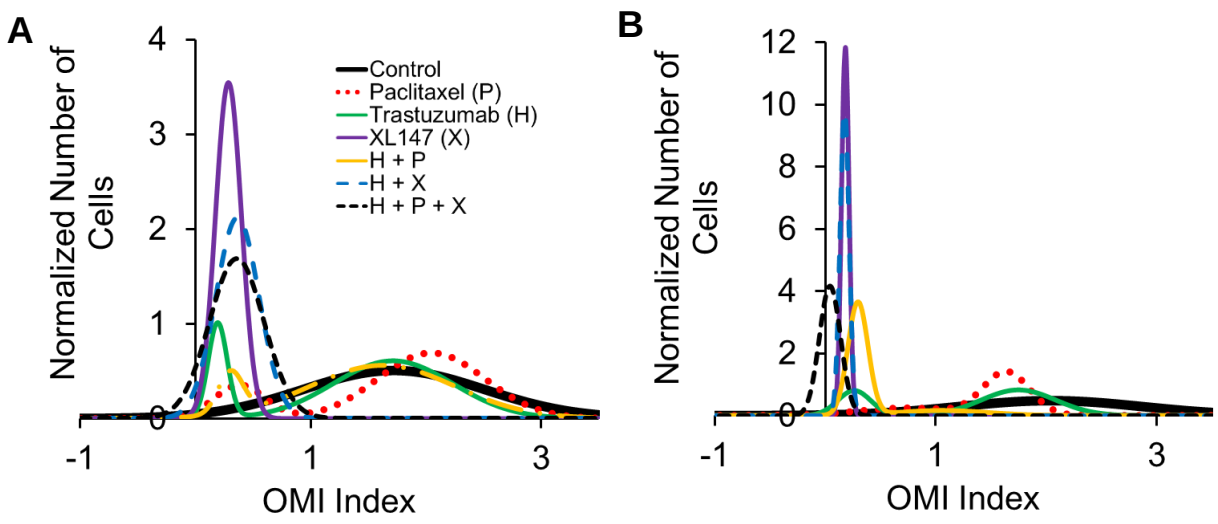
Supplementary Figure 1: OMI endpoints of organoids derived from a trastuzumab-responsive xenograft tumor. A. Redox ratio of BT474 xenograft-derived organoids treated with paclitaxel (P), trastuzumab (H), XL147 (X), and the combined drug treatments H+P, H+X, H+P+X at 24 (blue), 48 (red), and 72hr (green). B. NADH τ_m of BT474 xenograft-derived drug treated organoids at 24 (blue), 48 (red), and 72hr (green). C. FAD τ_m of BT474 xenograft-derived drug treated organoids at 24 (blue), 48 (red), and 72hr (green). D. OMI index (composite endpoint of weighted redox ratio, NADH τ_m, and FAD τ_m) of BT474 xenograft-derived drug treated organoids at 24 (blue), 48 (red), and 72hr (green). *$p<0.05$, for treated vs. control within a time point.

Supplementary Table 1: NADH and FAD lifetime component values of BT474-xenograft derived organoids (mean, standard deviation) from a two-component exponential fit of the fluorescence decay, ($I(t) = \alpha_1 \exp^{-t/\tau_1} + \alpha_2 \exp^{-t/\tau_2} + C$). Boxes shaded pink represent a significant decrease in mean value vs. control. Boxes shaded blue represent a significant increase in mean value vs. control. NADH τ_1/α_1 is attributed to free NADH, NADH τ_2/α_2 is attributed to bound NADH. FAD τ_1/α_1 is attributed to bound FAD, FAD τ_2/α_2 is attributed to free FAD.

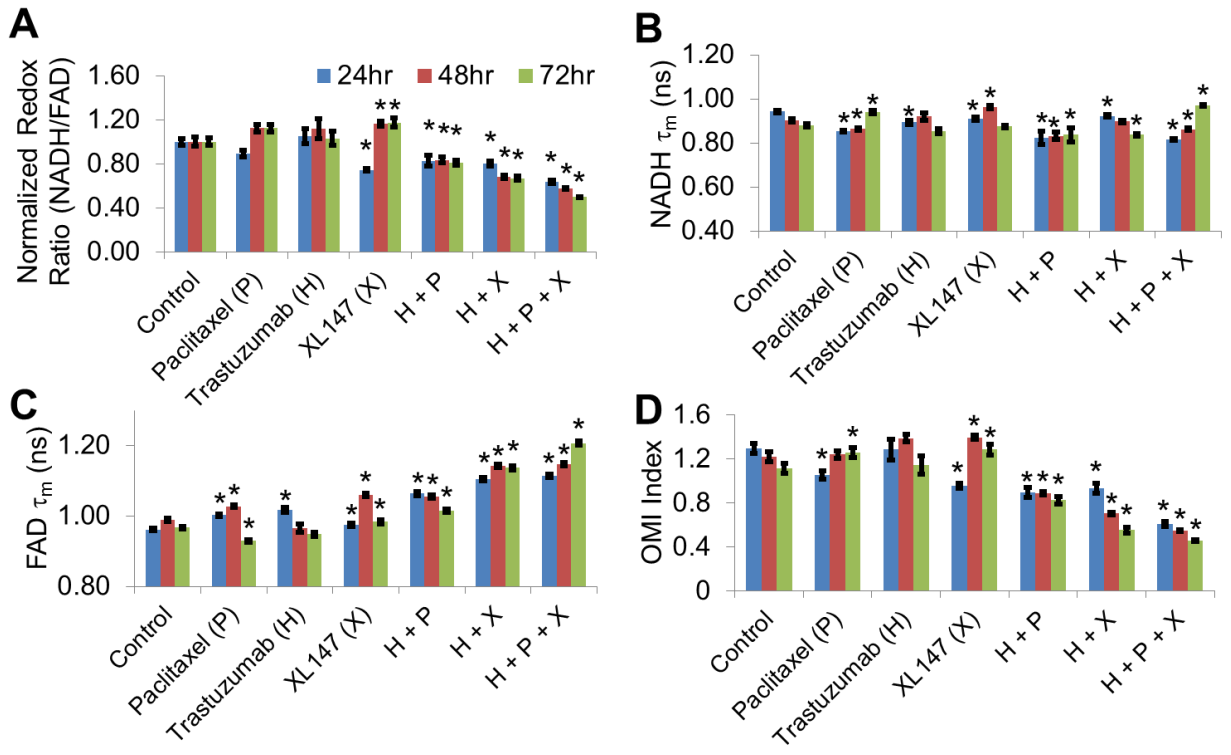
24 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	489	52	2743	135	69.2	2.9	368	36	2545	96	68.9	4.2
Paclitaxel (P)	430	45	2577	120	72.0	2.7	401	66	2521	163	71.0	5.1
Trastuzumab(H)	451	53	2652	112	70.5	2.5	383	30	2555	70	67.8	3.9
XL147(X)	474	17	2446	82	71.2	2.4	472	51	2430	91	67.8	2.2
H + P	452	46	2615	104	69.2	2.6	335	32	2505	85	71.5	4.7
H + X	476	28	2264	66	71.4	3.0	443	32	2231	87	70.3	4.0
H + P + X	452	29	2403	131	69.9	2.8	440	36	2373	74	66.9	2.7

48 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	438	39	2569	97	68.3	2.7	355	31	2476	84	68.4	3.6
Paclitaxel (P)	415	43	2496	113	70.7	2.1	341	40	2457	79	70.5	3.9
Trastuzumab(H)	434	40	2548	92	67.6	2.9	361	37	2495	88	66.3	4.2
XL147(X)	416	22	1976	51	75.4	2.0	467	45	2184	49	73.5	2.5
H + P	398	49	2515	106	70.9	2.7	371	30	2522	89	68.7	4.6
H + X	439	10	2320	51	73.3	1.8	425	11	2306	62	69.6	1.7
H + P + X	405	27	2255	134	70.0	2.6	434	40	2324	56	67.4	2.7

72 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	509	39	2721	81	64.7	3.5	368	34	2518	57	74.6	3.1
Paclitaxel (P)	480	39	2639	95	69.2	2.5	470	32	2588	70	63.7	2.3
Trastuzumab(H)	472	47	2606	103	67.4	2.8	499	63	2623	93	66.0	4.9
XL147(X)	475	18	2320	89	80.9	1.9	601	26	2719	96	76.8	1.4
H + P	391	47	2440	113	65.6	4.1	489	42	2660	113	61.2	5.2
H + X	441	37	2325	90	77.1	2.0	568	40	2523	90	69.2	1.6
H + P + X	392	18	2247	66	71.3	2.5	630	52	2680	116	66.4	4.1



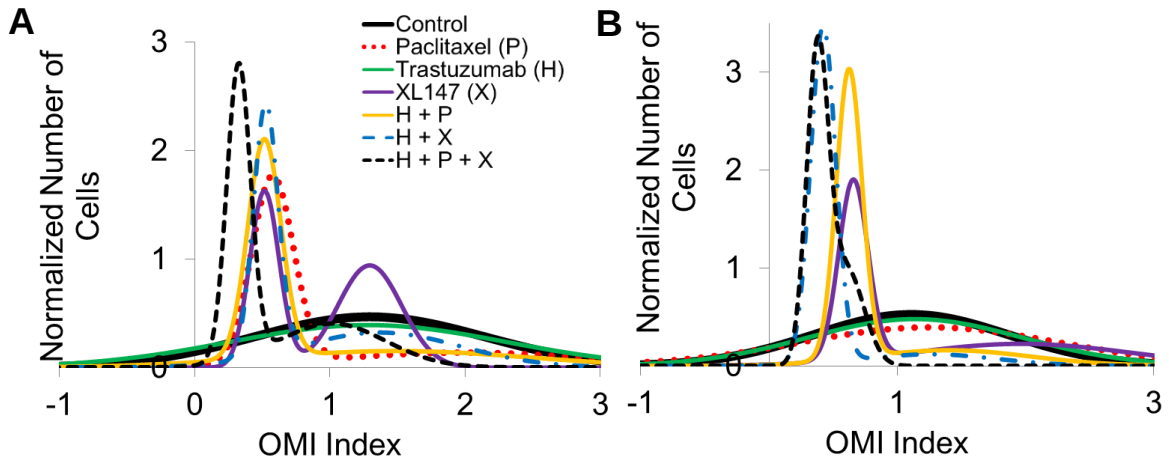
Supplementary Figure 2: Population modeling identifies heterogeneous drug responses of BT474 cells. A. Population density modeling of the mean OMI index per cell in control and treated BT474 organoids at 24 hr. B. Population density modeling of the OMI index for BT474 organoids treated for 72hr.



Supplementary Figure 3: OMI endpoints of organoids derived from a trastuzumab-resistant xenograft tumor. A. Redox ratio of HR6 xenograft-derived organoids treated with paclitaxel (P), trastuzumab (H), XL147 (X), and the combined drug treatments H+P, H+X, H+P+X at 24 (blue), 48 (red), and 72hr (green). B. NADH τ_m of HR6 xenograft-derived drug treated organoids at 24 (blue), 48 (red), and 72hr (green). C. FAD τ_m of HR6 xenograft-derived drug treated organoids at 24 (blue), 48 (red), and 72hr (green). D. OMI index (composite endpoint of weighted redox ratio, NADH τ_m, and FAD τ_m) of HR6 xenograft-derived drug treated organoids at 24 (blue), 48 (red), and 72hr (green). *$p<0.05$, for treated vs. control within a time point.

Supplementary Table 2: NADH and FAD lifetime component values of HR6-xenograft derived organoids (mean, standard deviation) from a two-component exponential fit of the fluorescence decay, ($I(t) = \alpha_1 \exp^{-t/\tau_1} + \alpha_2 \exp^{-t/\tau_2} + C$). Boxes shaded pink represent a significant decrease in mean value vs. control. Boxes shaded blue represent a significant increase in mean value vs. control. NADH τ_1/α_1 is attributed to free NADH, NADH τ_2/α_2 is attributed to bound NADH. FAD τ_1/α_1 is attributed to bound FAD, FAD τ_2/α_2 is attributed to free FAD.

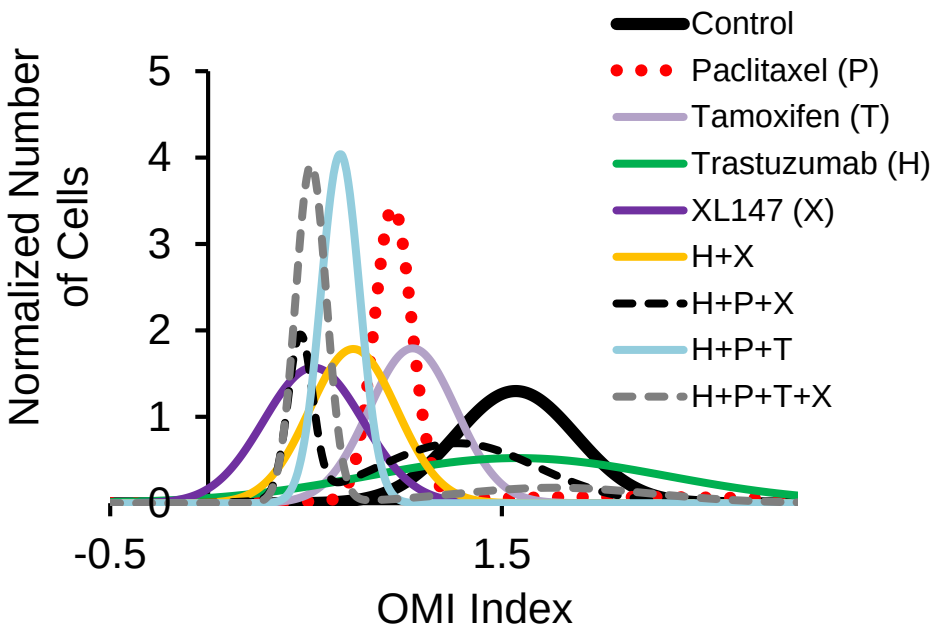
24 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	377	53	2518	144	74.2	3.0	399	31	2493	77	73.7	2.6
Paclitaxel (P)	322	44	2384	137	74.8	2.9	404	29	2456	82	70.6	2.8
Trastuzumab(H)	343	44	2446	138	73.8	2.3	396	30	2497	60	70.2	2.6
XL147(X)	371	57	2438	148	74.1	3.4	406	24	2409	83	71.6	2.3
H + P	326	38	2386	137	76.0	2.4	420	24	2486	78	68.7	2.5
H + X	367	39	2490	123	73.8	2.4	449	34	2539	75	68.5	2.6
H + P + X	340	41	2348	132	76.3	2.7	456	36	2487	74	67.5	2.8
48 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	375	45	2487	139	74.7	2.9	401	29	2485	78	72.2	2.3
Paclitaxel (P)	342	44	2395	140	74.8	2.7	409	30	2480	79	69.8	2.7
Trastuzumab(H)	364	50	2425	151	73.1	3.1	382	31	2459	54	71.8	3.2
XL147(X)	396	52	2480	132	72.8	2.9	431	25	2442	64	68.6	2.6
H + P	339	41	2380	146	75.9	2.2	435	27	2496	74	69.7	2.4
H + X	369	53	2397	172	74.0	2.5	471	30	2537	81	67.4	2.4
H + P + X	358	45	2331	128	74.4	3.2	476	36	2526	83	67.1	2.8
72 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	379	47	2462	148	76.1	3.1	407	31	2473	79	72.7	2.3
Paclitaxel (P)	348	58	2374	195	75.4	3.8	377	29	2409	73	72.6	2.6
Trastuzumab(H)	351	46	2358	151	75.1	2.6	377	30	2408	64	71.8	2.2
XL147(X)	345	43	2379	139	74.0	2.8	387	28	2426	75	70.6	3.1
H + P	337	37	2364	137	75.4	2.6	400	31	2472	80	70.2	2.2
H + X	336	34	2308	118	74.6	2.5	453	26	2472	73	66.0	2.7
H + P + X	418	26	2354	75	71.3	3.1	485	26	2587	96	65.6	3.0



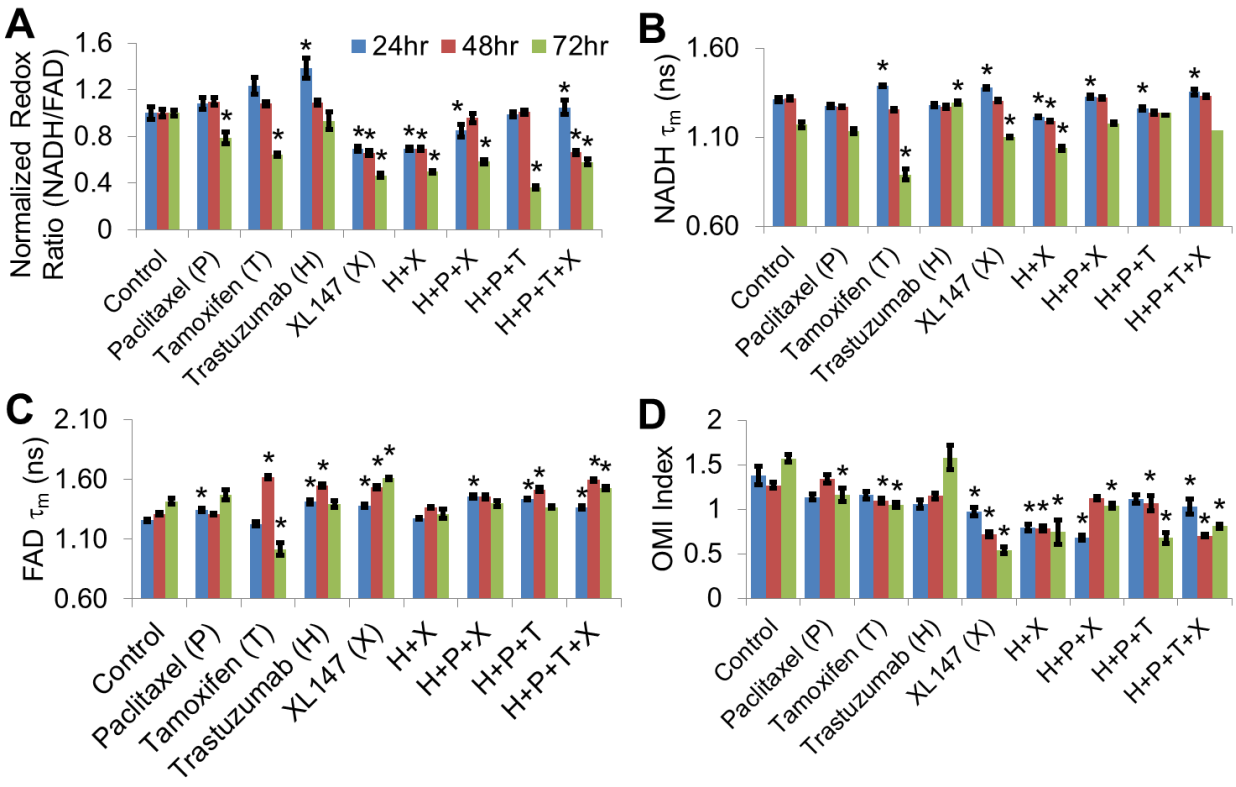
Supplementary Figure 4: **Population modeling identifies heterogeneous drug responses of HR6 cells.** A. Population density modeling of the mean OMI index per cell in control and treated HR6 organoids at 24 hr. B. Population density modeling of the OMI index for HR6 organoids treated for 72hr.

Supplementary Table 3: Grade, proliferation rate, estrogen receptor expression, progesterone receptor expression, and HER2 receptor expression of the patient samples.

Sample	Grade	Proliferative rate	ER intensity	ER % stained cells	PR intensity	PR % stained cells	Her2 FISH	Her2:Cep17 ratio	Figures
1	high	high	3+	95	3+	95	Not Amp	1.7	Fig. 5A-C, Sup. Fig. 3
2	Intermediate	intermediate	3+	90	3+	90	Not Amp	1.4	Fig. 5D,E Sup. Fig. 4
3	high	high	3+	95	3+	99	Not Amp	1	Fig. 5F,G Sup. Fig. 5
4	high	intermediate	3+	95	3+	70	Not Amp	1.1	Fig. 5H,I Sup. Fig. 6
5	high	high	0	0	0	0	Amp	7.95	Fig. 6A,B Sup. Fig. 7
6	high	high	2+	3	2+	3	Not Amp	0.9	Fig. 6C,D Sup. Fig. 8



Supplementary Figure 5: **Population modeling identifies heterogeneous drug responses of organoids from patient sample #1 (ER+/HER2-).** Population density modeling of the mean OMI index per cell in control and treated organoids derived from patient sample #1 (ER+/HER2+) at 72 hr.



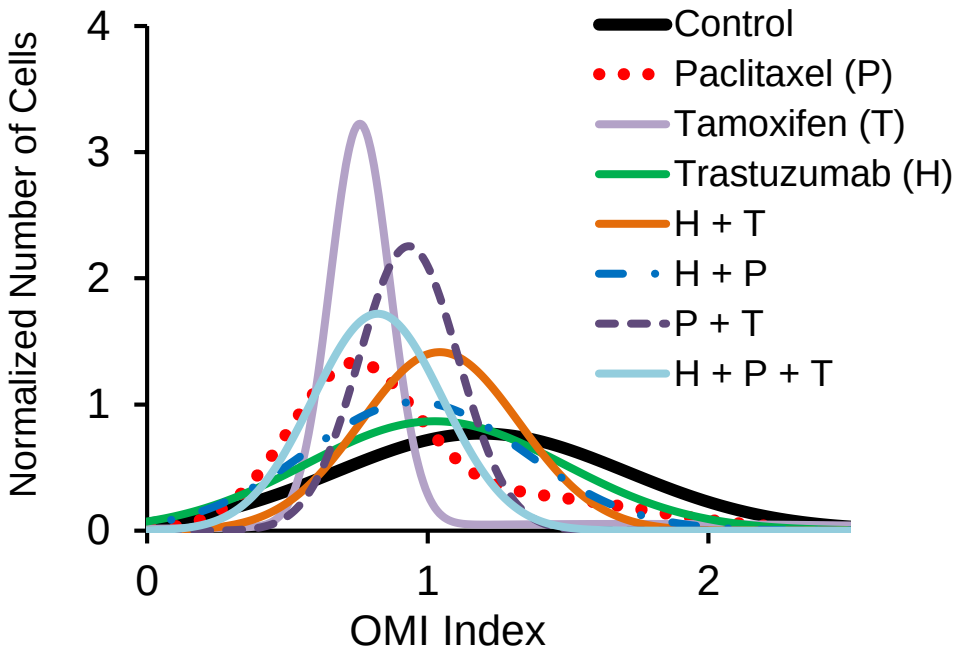
Supplementary Figure 6: OMI endpoints of organoids derived from a ER+ primary tumor. A. Redox ratio of organoids derived from an ER+ primary tumor treated with paclitaxel (P), tamoxifen (T), trastuzumab (H), XL147 (X), and the combined drug treatments H+X, H+P+X, H+P+T, and H+P+T+X at 24 (blue), 48 (red), and 72hr (green). B. NADH τ_m of organoids derived from an ER+ primary tumor at 24 (blue), 48 (red), and 72hr (green). C. FAD τ_m of organoids derived from an ER+ primary tumor at 24 (blue), 48 (red), and 72hr (green). D. OMI index (composite endpoint of weighted redox ratio, NADH τ_m, and FAD τ_m) of organoids derived from an ER+ primary tumor at 24 (blue), 48 (red), and 72hr (green). *$p<0.05$, for treated vs. control within a time point.

Supplementary Table 4: NADH and FAD lifetime component values of organoids derived from an ER+ primary tumor (mean, standard deviation). Boxes shaded pink represent a significant decrease in mean value vs. control. Boxes shaded blue represent a significant increase in mean value vs. control. NADH τ_1/α_1 is attributed to free NADH, NADH τ_2/α_2 is attributed to bound NADH. FAD τ_1/α_1 is attributed to bound FAD, FAD τ_2/α_2 is attributed to free FAD.

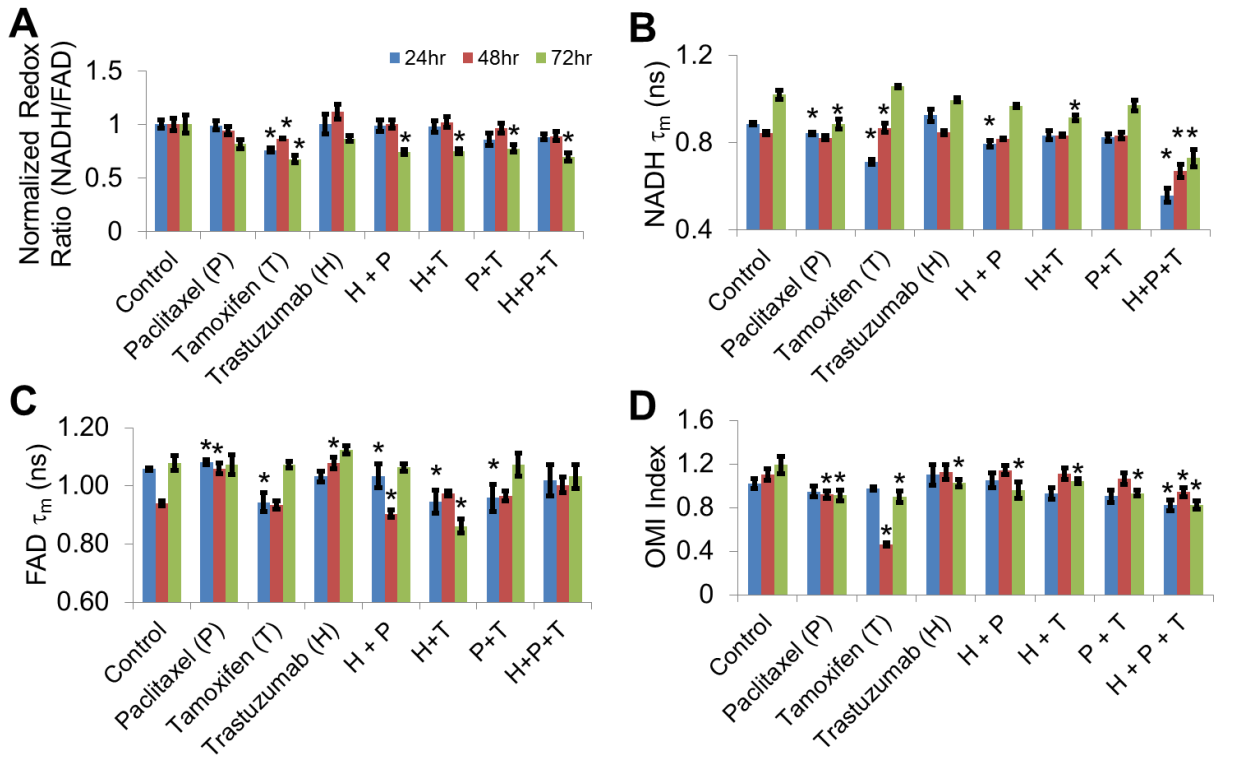
24 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	566	81	2715	142	64.5	2.3	428	53	2676	124	62.7	4.1
Paclitaxel (P)	518	50	2623	110	63.2	2.6	466	78	2693	148	60.0	3.9
Tamoxifen (T)	571	128	2745	247	61.7	3.1	428	81	2613	157	63.0	5.5
Trastuzumab(H)	521	42	2579	112	62.5	3.6	505	60	2759	125	59.2	5.5
XL147 (X)	643	42	2499	176	60.1	1.8	610	71	2645	102	62.1	4.3
H + X	537	34	2418	135	63.5	3.2	493	33	2560	85	62.0	4.6
H + P +X	584	50	2516	143	59.7	3.7	604	76	2711	117	59.9	3.9
H + P + T	470	25	2551	121	61.5	2.2	493	39	2714	90	57.2	2.2
H + P + T + X	573	54	2585	160	60.7	2.8	547	76	2688	141	63.3	5.8

48 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	545	42	2596	110	61.7	1.8	454	40	2693	98	61.4	2.9
Paclitaxel (P)	565	32	2643	116	65.0	2.6	496	45	2746	116	63.0	4.2
Tamoxifen (T)	476	33	2479	65	60.6	2.4	652	84	2937	171	57.0	2.2
Trastuzumab(H)	493	54	2466	136	61.5	4.7	615	96	2865	187	58.3	4.5
XL147 (X)	595	26	2465	112	61.7	2.9	733	77	2852	131	61.9	2.7
H + X	523	31	2395	91	64.0	3.3	553	46	2639	91	60.8	4.5
H + P +X	573	36	2524	147	61.1	4.0	660	101	2772	149	62.2	4.7
H + P + T	480	24	2437	57	60.9	2.7	557	51	2771	95	56.3	2.2
H + P + T + X	564	33	2465	73	59.4	1.9	723	59	2871	102	59.0	2.5

72 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	446	54	2463	104	63.9	3.6	535	94	2788	166	61.4	4.5
Paclitaxel (P)	429	48	2403	94	63.7	3.4	567	144	2820	287	60.0	9.4
Tamoxifen (T)	347	230	2471	384	74.5	5.3	358	246	2627	306	70.8	8.8
Trastuzumab(H)	577	56	2826	187	67.2	2.3	546	68	2846	168	62.3	4.9
XL147 (X)	428	17	2282	63	63.6	2.6	778	57	2875	95	60.2	1.7
H + X	392	34	2267	70	65.5	3.8	535	135	2639	145	62.9	7.3
H + P +X	475	21	2461	127	64.3	3.5	676	119	2755	200	65.6	4.4
H + P + T	622	51	2866	164	71.6	1.7	554	34	2807	111	63.0	1.9
H + P + T + X	416	22	2348	123	62.1	2.9	704	91	2870	150	61.6	4.8



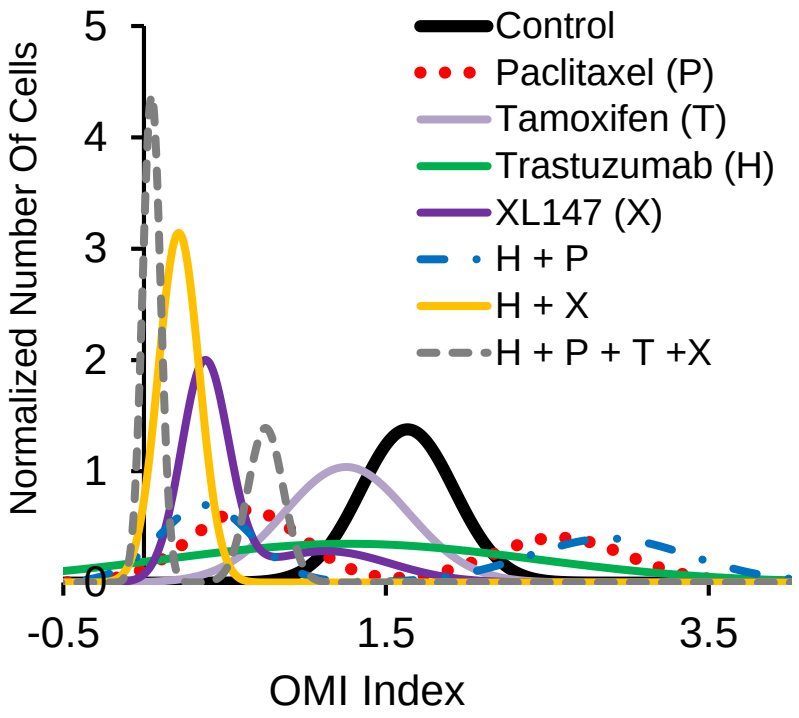
Supplementary Figure 7: **Population modeling identifies heterogeneous drug responses of organoids from patient sample #2 (ER+/HER2-).** Population density modeling of the mean OMI index per cell in control and treated organoids derived from patient sample #2 (ER+/HER2+) at 72 hr.



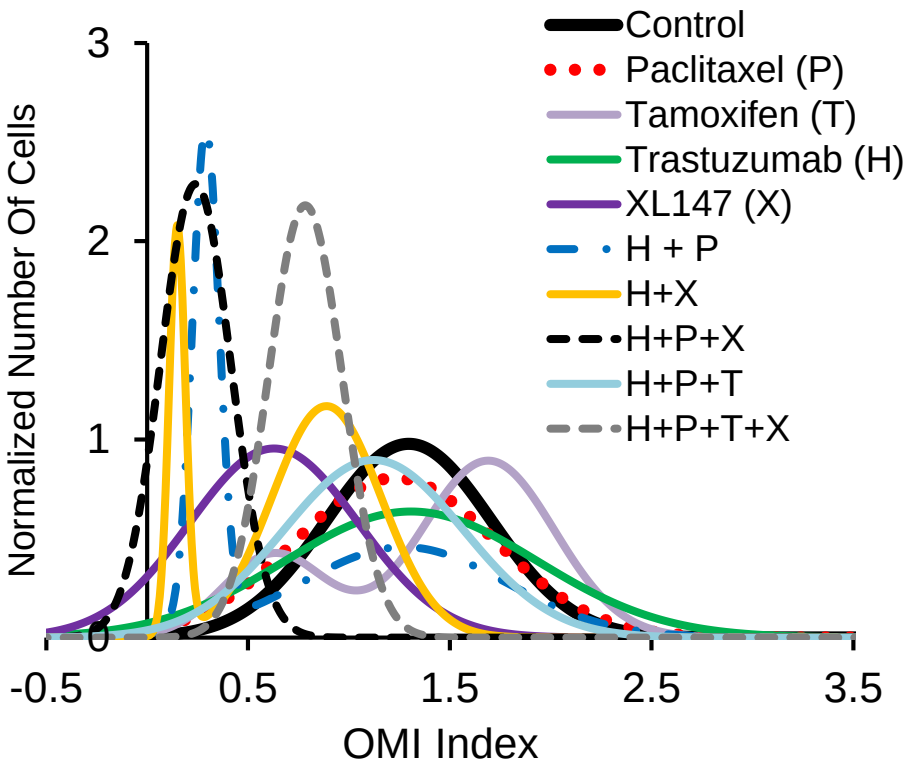
Supplementary Figure 8: OMI endpoints of organoids derived from a second ER+ primary tumor. A. Redox ratio of organoids derived from a second ER+ primary tumor treated with paclitaxel (P), tamoxifen (T), trastuzumab (H), and the combined drug treatments H+P, H+T, P+T, and H+P+T at 24 (blue), 48 (red), and 72hr (green). B. NADH τ_m at 24 (blue), 48 (red), and 72hr (green). C. FAD τ_m at 24 (blue), 48 (red), and 72hr (green). D. OMI index (composite endpoint of weighted redox ratio, NADH τ_m, and FAD τ_m) at 24 (blue), 48 (red), and 72hr (green). *$p<0.05$, for treated vs. control within a time point.

Supplementary Table 5: NADH and FAD lifetime component values of organoids derived from a second ER+ primary tumor (mean, standard deviation). Boxes shaded pink represent a significant decrease in mean value vs. control. Boxes shaded blue represent a significant increase in mean value vs. control. NADH τ_1/α_1 is attributed to free NADH, NADH τ_2/α_2 is attributed to bound NADH. FAD τ_1/α_1 is attributed to bound FAD, FAD τ_2/α_2 is attributed to free FAD.

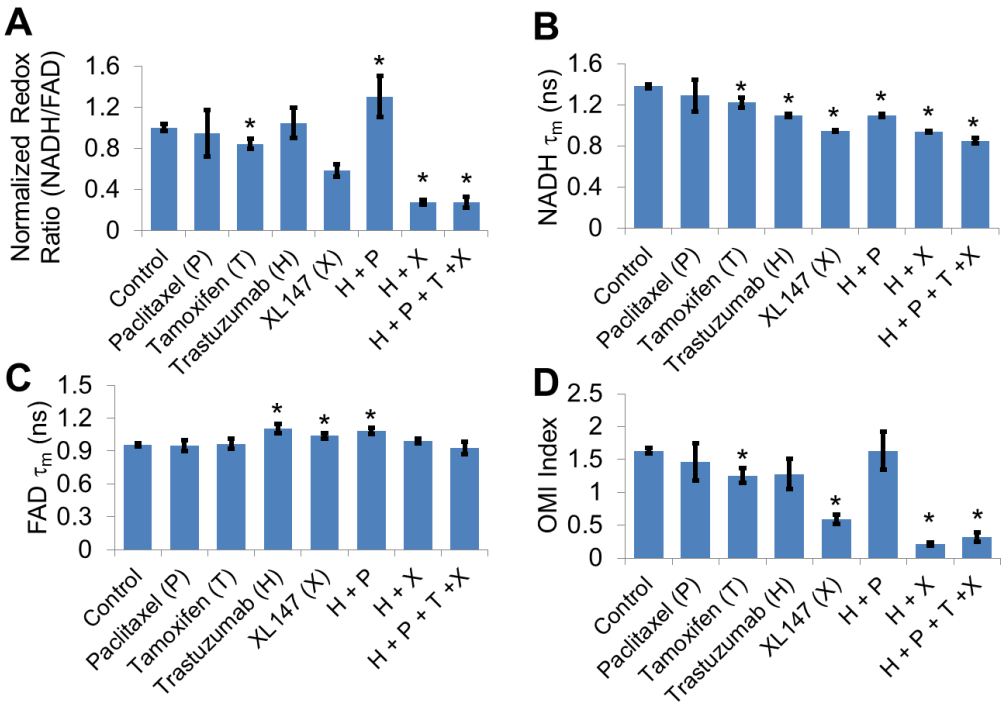
24 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	338	45	2571	133	75.4	1.7	429	35	2504	91	69.2	2.1
Paclitaxel (P)	304	28	2502	76	75.3	1.2	432	42	2453	99	67.4	2.8
Tamoxifen (T)	284	45	2379	96	79.6	3.1	242	67	2217	146	79.4	8.0
Trastuzumab(H)	406	182	2624	288	76.6	2.4	396	44	2537	102	70.2	3.8
H + T	306	19	2494	65	75.8	3.2	343	57	2373	80	70.2	4.8
H + P	282	24	2495	119	76.8	2.0	385	69	2492	162	68.9	5.7
P + T	295	26	2483	46	75.9	1.8	347	60	2381	63	69.8	5.2
H + P + T	280	22	2487	134	76.9	1.7	393	98	2442	188	69.2	5.7
48 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	331	34	2438	119	75.7	2.6	373	52	2421	125	70.6	3.6
Paclitaxel (P)	309	49	2438	110	76.6	4.0	409	72	2438	160	67.6	4.9
Tamoxifen (T)	296	29	2639	101	75.2	1.3	548	177	3129	486	59.3	7.5
Trastuzumab(H)	306	40	2520	154	75.3	2.6	426	90	2562	224	68.8	4.5
H + T	316	19	2481	119	76.2	1.7	396	45	2344	105	70.2	2.7
H + P	325	35	2429	138	76.5	2.7	339	55	2434	170	72.9	4.0
P + T	316	42	2467	163	76.0	3.9	363	51	2446	131	71.0	4.1
H + P + T	314	41	2432	142	75.9	4.0	378	56	2458	140	69.7	5.8
72 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	397	54	2496	143	71.0	4.5	418	87	2485	218	67.4	5.7
Paclitaxel (P)	352	72	2488	206	74.2	6.3	400	128	2518	263	67.8	9.2
Tamoxifen (T)	431	72	2500	190	69.7	3.0	420	57	2370	110	66.2	4.3
Trastuzumab(H)	392	50	2547	158	71.9	4.4	415	101	2533	239	66.0	6.6
H + T	368	63	2474	127	74.0	5.2	325	113	2395	265	74.2	8.1
H + P	375	58	2495	147	72.4	4.7	399	91	2447	221	67.7	6.3
P + T	376	60	2492	163	71.9	4.9	400	89	2478	228	67.3	7.7
H + P + T	352	76	2488	175	73.5	6.4	400	111	2485	228	69.0	7.7



Supplementary Figure 9: **Population modeling identifies heterogeneous drug responses of organoids from patient sample #3 (ER+/HER2-).** Population density modeling of the mean OMI index per cell in control and treated organoids derived from patient sample #3 (ER+/HER2+) at 24 hr.



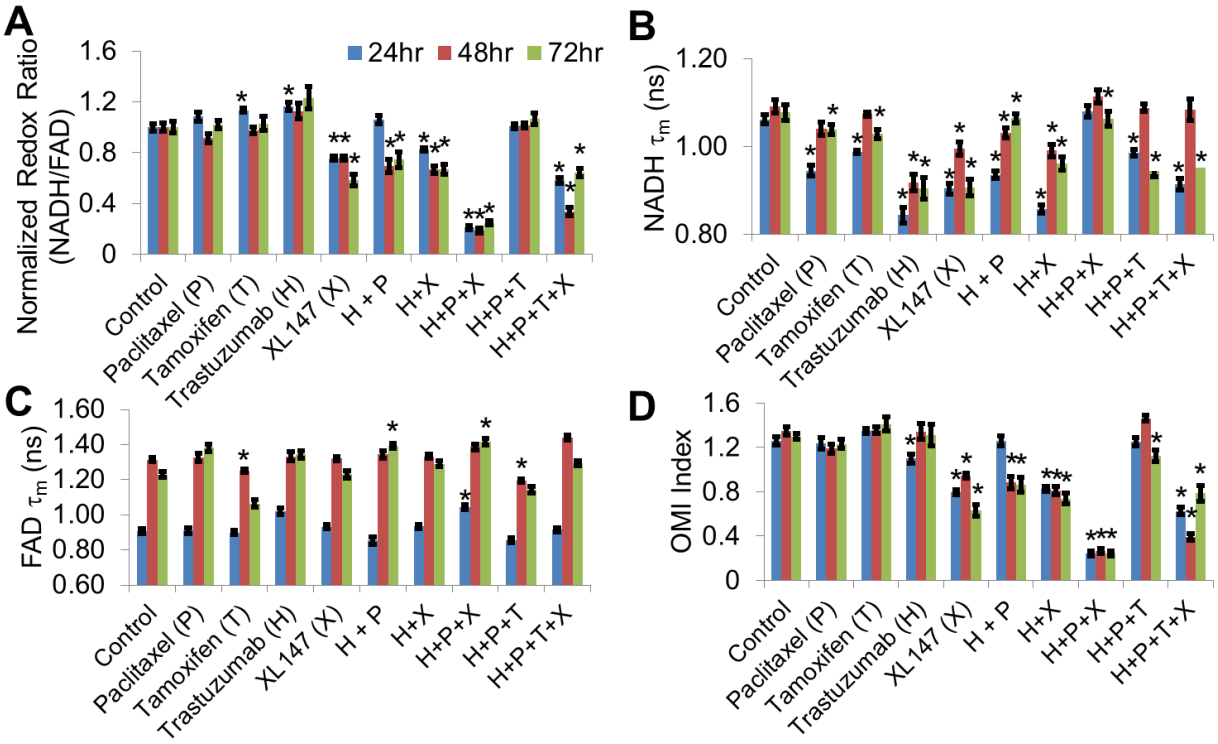
Supplementary Figure 10: **Population modeling identifies heterogeneous drug responses of organoids from patient sample #4 (ER+/HER2-).** Population density modeling of the mean OMI index per cell in control and treated organoids derived from patient sample #4 (ER+/HER2+) at 72 hr.



Supplementary Figure 11: OMI endpoints of organoids derived from a third ER+ primary tumor. A. Redox ratio of organoids derived from a third ER+ primary tumor treated with paclitaxel (P), tamoxifen (T), trastuzumab (H), XL147 (X) and the combined drug treatments H+P, H+X, and H+P+T+X at 24hr. B. NADH τ_m of these organoids at 24hr. C. FAD τ_m of these organoids at 24hr. D. OMI index (composite endpoint of weighted redox ratio, NADH τ_m, and FAD τ_m) at 24hr. *p<0.05, for treated vs. control.

Supplementary Table 6: NADH and FAD lifetime component values of organoids derived from a third ER+ primary tumor (mean, standard deviation). Boxes shaded pink represent a significant decrease in mean value vs. control. Boxes shaded blue represent a significant increase in mean value vs. control. NADH τ_1/α_1 is attributed to free NADH, NADH τ_2/α_2 is attributed to bound NADH. FAD τ_1/α_1 is attributed to bound FAD, FAD τ_2/α_2 is attributed to free FAD.

24 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	311	143	2546	189	73.6	6.8	396	56	2628	134	74.9	2.0
Paclitaxel (P)	632	354	2946	709	70.8	6.4	373	118	2656	185	74.3	3.1
Tamoxifen (T)	444	27	2655	39	64.6	3.7	449	179	2665	347	76.1	3.3
Trastuzumab(H)	392	39	2631	85	68.3	5.3	409	37	2593	79	67.6	9.5
XL147 (X)	423	16	2320	87	72.3	3.2	440	47	2361	147	68.9	4.2
H + P	412	48	2587	87	68.5	2.0	413	58	2629	119	69.0	4.9
H + X	417	13	2238	58	71.3	3.7	445	45	2353	121	71.4	3.9
H + P + T + X	442	27	2150	50	68.7	4.4	385	154	2375	245	73.0	7.0



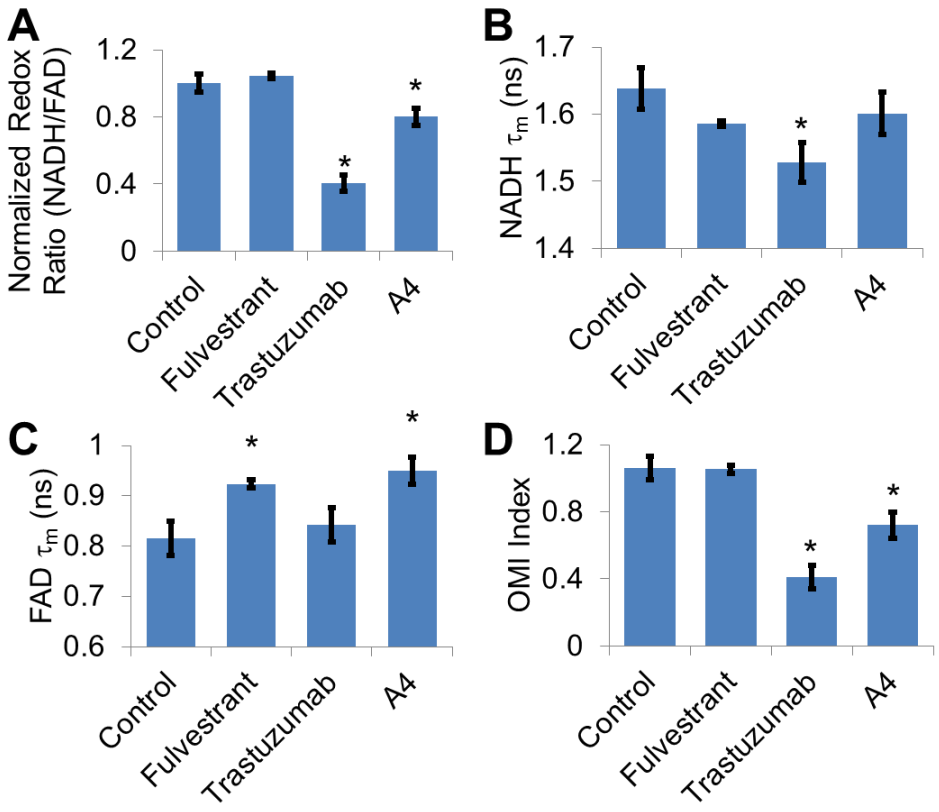
Supplementary Figure 12: OMI endpoints of organoids derived from a fourth ER+ primary tumor. A. Redox ratio of organoids derived from a fourth ER+ primary tumor treated with paclitaxel (P), tamoxifen (T), trastuzumab (H), XL147 (X) and the combined drug treatments H+P, H+X, H+P+X, H+P+T, and H+P+T+X at 24 (blue), 48 (red), and 72hr (green). B. NADH τ_m of these organoids at 24 (blue), 48 (red), and 72hr (green). C. FAD τ_m at 24 (blue), 48 (red), and 72hr (green). D. OMI index (composite endpoint of weighted redox ratio, NADH τ_m, and FAD τ_m) at 24 (blue), 48 (red), and 72hr (green). *$p<0.05$, for treated vs. control within a time point.

Supplementary Table 7: NADH and FAD lifetime component values of organoids derived from a fourth ER+ primary tumor (mean, standard deviation). Boxes shaded pink represent a significant decrease in mean value vs. control. Boxes shaded blue represent a significant increase in mean value vs. control. NADH τ_1/α_1 is attributed to free NADH, NADH τ_2/α_2 is attributed to bound NADH. FAD τ_1/α_1 is attributed to bound FAD, FAD τ_2/α_2 is attributed to free FAD.

24 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	475	13	2918	59	76.0	2.1	293	30	2627	101	73.2	3.0
Paclitaxel (P)	431	15	2722	58	77.6	2.8	291	43	2561	142	72.4	3.4
Tamoxifen (T)	441	17	2758	53	76.4	3.6	289	36	2560	131	72.8	2.9
Trastuzumab(H)	421	13	2664	74	81.3	3.7	326	46	2594	107	68.8	3.1
XL147 (X)	426	13	2683	75	78.9	3.9	323	31	2509	103	71.7	2.9
H + P	425	17	2778	83	78.3	3.7	293	70	2516	204	74.6	5.1
H + X	417	15	2678	75	80.6	3.2	313	39	2495	115	71.2	3.2
H + P +X	450	18	2578	171	69.7	6.6	359	25	2467	74	67.4	3.6
H + P + T	440	13	2764	57	76.6	2.3	271	36	2535	116	73.8	4.4
H + P + T + X	431	12	2749	77	79.2	2.4	327	25	2434	87	71.7	2.7

48 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	517	23	2934	70	76.2	3.8	536	57	2966	156	66.1	3.5
Paclitaxel (P)	475	36	2769	89	75.3	5.3	565	92	2966	265	67.0	5.8
Tamoxifen (T)	485	25	2821	54	74.8	4.0	515	40	2884	125	67.8	3.8
Trastuzumab(H)	448	21	2710	73	79.3	3.9	561	82	2918	210	65.7	3.2
XL147 (X)	475	28	2764	73	77.3	3.5	584	46	2883	144	66.7	2.8
H + P	444	42	2742	131	74.1	8.1	551	98	2875	236	64.6	4.8
H + X	458	20	2717	100	76.1	7.1	605	62	2878	188	66.7	5.7
H + P +X	472	13	2581	164	68.9	6.7	610	49	2732	104	63.0	3.2
H + P + T	480	14	2834	48	74.1	2.5	493	54	2897	155	69.7	3.2
H + P + T + X	464	19	2645	128	71.0	9.1	616	56	2817	119	61.7	3.6

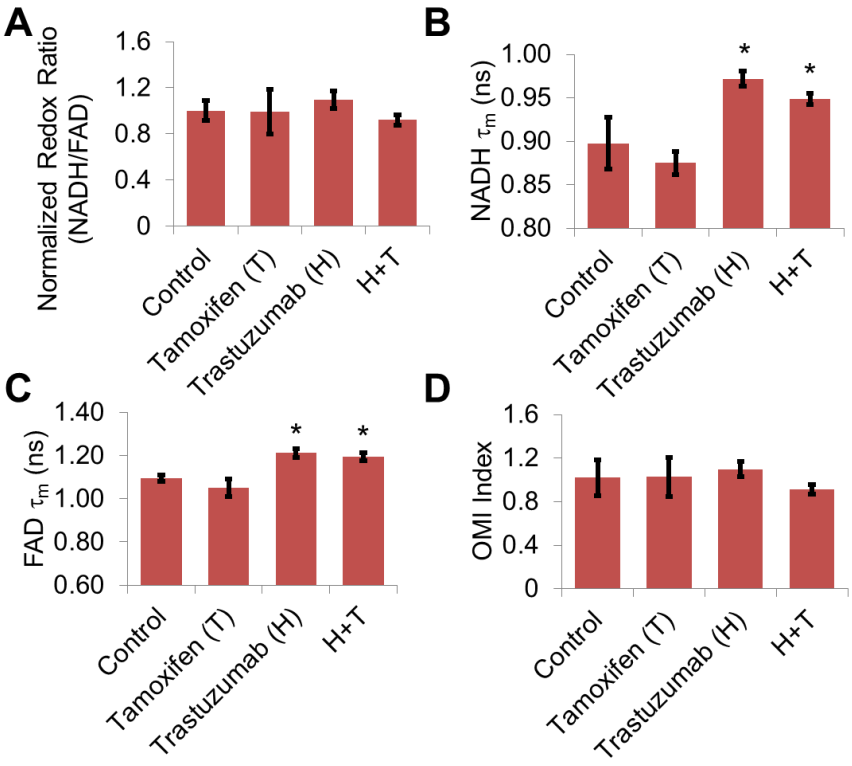
72 hr	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	475	54	2815	137	74.2	4.5	506	71	2908	207	69.1	4
Paclitaxel (P)	516	136	2782	204	73.8	4.2	648	200	3134	406	68.9	4.2
Tamoxifen (T)	414	59	2658	130	72.7	5.6	433	89	2702	214	71.6	4.7
Trastuzumab(H)	400	17	2585	73	77	6.8	550	85	2922	265	65.1	5.3
XL147 (X)	398	39	2551	100	76.3	6.5	543	91	2730	173	67.8	5.9
H + P	420	35	2659	109	70.9	7.8	590	92	2940	276	64.5	6.2
H + X	407	21	2602	91	74.6	6.4	554	45	2779	119	65.8	5.7
H + P +X	454	24	2572	147	70.6	7.4	644	68	2783	140	63.2	3.6
H + P + T	405	23	2597	93	75.3	5.2	464	85	2746	225	69.4	5.4
H + P + T + X	444	23	2735	105	77.7	5	590	52	2791	130	66.9	3.5



Supplementary Figure 13: OMI endpoints of organoids derived from a HER2+ primary tumor. A. Redox ratio of organoids derived from a HER2+ primary tumor treated with fulvestrant, trastuzumab, and A4 at 24hr. B. NADH τ_m of these organoids at 24hr. C. FAD τ_m at 24hr. D. OMI index (composite endpoint of weighted redox ratio, NADH τ_m, and FAD τ_m) at 24hr. *p<0.05, for treated vs. control.

Supplementary Table 8: NADH and FAD lifetime component values of organoids derived from a HER2+ primary tumor (mean, standard deviation). Boxes shaded pink represent a significant decrease in mean value vs. control. Boxes shaded blue represent a significant increase in mean value vs. control. NADH τ_1/α_1 is attributed to free NADH, NADH τ_2/α_2 is attributed to bound NADH. FAD τ_1/α_1 is attributed to bound FAD, FAD τ_2/α_2 is attributed to free FAD.

	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	642	129	2923	171	57.5	6.0	389	62	2479	249	78.5	3.8
Fulvestrant (F)	631	78	2889	119	57.4	3.0	412	65	2565	194	75.7	3.2
Trastuzumab(H)	651	76	2922	119	56.4	2.4	383	65	2529	199	78.2	3.4
A4	619	90	2864	145	56.0	2.5	400	57	2634	158	74.8	3.3



Supplementary Figure 14: OMI endpoints of organoids derived from a TNBC primary tumor. A. Redox ratio of organoids derived from a TNBC primary tumor treated with tamoxifen (T), trastuzumab (H), and the combined treatment, H+T at 48hr. B. NADH τ_m of these organoids at 48hr. C. FAD τ_m at 48hr. D. OMI index (composite endpoint of weighted redox ratio, NADH τ_m, and FAD τ_m) at 48hr. *$p<0.05$, for treated vs. control.

Supplementary Table 9: NADH and FAD lifetime component values of organoids derived from a TNBC primary tumor (mean, standard deviation). Boxes shaded pink represent a significant decrease in mean value vs. control. Boxes shaded blue represent a significant increase in mean value vs. control. NADH τ_1/α_1 is attributed to free NADH, NADH τ_2/α_2 is attributed to bound NADH. FAD τ_1/α_1 is attributed to bound FAD, FAD τ_2/α_2 is attributed to free FAD.

	NADH τ_1 (ps)		NADH τ_2 (ps)		NADH α_1		FAD τ_1 (ps)		FAD τ_2 (ps)		FAD α_1	
	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std	Mean	std
Control	379	50	2423	121	74.7	3.6	393	41	2512	56	66.5	2.6
Tamoxifen (T)	361	89	2454	217	75.0	2.7	364	42	2449	69	67.4	4.3
Trastuzumab (H)	319	25	2542	65	70.4	2.3	375	42	2578	103	61.7	4.4
A4	338	16	2487	55	71.5	1.9	415	41	2530	71	62.9	4.1